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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1743	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,775	MATTIASSON ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1743	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-25* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claim 10 provides for the use of a sensor according to claim 6, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

2. Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

3. For the purposes of examination a capacitive sensor is being treated as the metal electrode with a self assembled recognition layer immobilized thereon.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1 and 3-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilpert (EP 263948) in view of the abstract of the Berggren paper and Fowlkes (US 5,935,823), Kay (US 5,498,538), Lopez (US 5972,656) or Wylie (US 6,111,079). In the published application Hilpert teaches a biosensor. The biosensor comprises a reactive biochemical component, especially a phytochelatin peptide, immobilized on a transducer. Suitable transducers are field effect transistor units, with a layer of phytochelatin immobilized on the gate; piezoelectric crystals coated with a layer of immobilized phytochelatin; and optical conductors with a layer of

immobilized phytochelatin. On contact with aqueous solutions of heavy metal ions, complexes with the phytochelatin lead to a change in the transducer output, so that the devices provide a rapid means of analysis of heavy metal ions. The phytochelatins are being treated as functional derivatives of the specific sequences claimed in claim 7. Hilpert does not teach the specifically claimed steps of how the peptides are immobilized on the transducers.

The abstract of the Berggren paper was published August 1, 1997 in *Advance ACS Abstracts* (see the last footnote on page 3657) and teaches capacitance measurements of antibody-antigen interactions in a flow system. Capacitive immunosensors were made by coupling monoclonal antibodies to thioctic acid, which had self-assembled on a gold electrode. Surface areas that were not covered were plugged with 1-dodecanethiol to make the layer dense and insulating. Cyclic voltammetry showed that the hexacyanoferrate redox reactions were blocked by this procedure. The capacitance of the electrode was evaluated from the current transients obtained when a potentiostatic step was applied. The immunosensor was placed in a flow system, and a capacitance decrease could be observed after injection of an unlabeled antigen. It was linear over almost three decades when plotted vs. the logarithm of the antigen concentration. Several analytes were determined with a detection limit of 1 pg/mL or better. Also cross reactivity was not seen for at least one case.

In the patent Fowlkes teaches heterofunctional binding fusion proteins termed totally synthetic affinity reagents (TSARS) that are concatenated heterofunctional polypeptides or proteins comprising at least two functional regions: a binding domain with affinity for a ligand that is characterized by 1) its strength of binding under specific conditions, 2) the stability of its binding under specific conditions, and 3) its selective specificity for the chosen ligand (see column 16, lines 1-5) and a second effector peptide portion that is chemically or biologically active. In one embodiment, the heterofunctional polypeptides or proteins further comprise a linker peptide portion between the binding domain and the second active peptide portion. The linker peptide can be either susceptible or not susceptible to cleavage by enzymatic or chemical means. Novel and/or improved heterofunctional binding reagents as well as methods for using the reagents for a variety of in vitro and in vivo applications are also disclosed. In column 5, lines 36-42 teach that the term phytochelatin was proposed for the major heavy metal binding peptides of higher plants [Grill et al., Science 230: 674 (1989)]. The structure of these small

peptides was determined to be NH_3^+-γGlu-Cys-γGlu-Cys-γGlu-Cys-γGlu-Cys-Gly-COO^- with minor components of $(\gamma Glu\text{-}Cys)_n$ Gly where n=3, 5, 6 or 7. The peptides were induced by and bound Cd^{++},Cu^{++}, Hg^{++}, Pb^{++} and Zn^{++}.

In the patent Kay has a disclosure that is similar to Fowlkes since they both claim benefit of the same patent application. Kay differs from Fowlkes as it discloses more peptides than Fowlkes.

In the patent Lopez teaches metal binding polypeptides which include an amino acid sequence coding for a variable region of a monoclonal antibody which immunoreacts with a mercury cation. The invention is also directed to fusion proteins which include a phage coat protein or portion thereof and the monoclonal antibody heavy chain variable region. The invention also provides bacteriophages which include the fusion protein in their coat. In addition, methods for detecting, removing, adding, or neutralizing mercuric cations in biological or inanimate systems through the use of the mercury binding polypeptides are provided. Column 4, lines 40-67 teach advantages that include a high specificity for the heavy metal. Column 5, lines 59-67 teach that these methods utilize features such as metal binding polypeptide immobilization, heavy metal immobilization, competitive binding, and means employing an oscillating probe, a micromagnetic probe and other physiochemical methods typically used to monitor antigen-antibody interactions. Column 6, lines 1-54 give more specific details on the detection methods.

In the patent Wylie teaches metal binding polypeptides which include an amino acid sequence coding for a light chain variable region of a monoclonal antibody capable of immunoreacting with a lead cation and nucleotides which include a nucleic acid sequence coding for the variable region are provided. The invention is also directed to fusion proteins and Fab fragments which include the light chain variable region. In addition, methods for detecting, removing, adding, or neutralizing lead cations in biological or inanimate systems through the use of the lead binding polypeptides are provided. Column 4, lines 31-61 teach advantages that include a high specificity for the heavy metal. Column 6, lines 7-56 teach that these methods utilize features such as metal binding polypeptide immobilization, heavy metal immobilization,

competitive binding, and means employing an oscillating probe, a micromagnetic probe and other physiochemical methods typically used to monitor antigen-antibody interactions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the detection compounds of Hilpert through a process as taught by Berggren because of the ability to attach a complexing peptide to the metal and cover the surface of the metal with a compound that will block its interaction with a sample as taught by Berggren. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the metal complexing peptides of Fowlkes, Kay, Lopez or Wylie or other well known peptides and protein having the ability to bind heavy metals for the phytochelatin of Hilpert because of there equivalence as taught by Fowlkes and Kay or their known selectivity towards the metal as taught by Lopez or Wylie.

6. Claims 1 and 3-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hilpert as explained above in view of Steinberg (1995, newly cited and applied), Duan (1995, newly cited and applied) and Fowlkes, Kay, Lopez or Wylie (last four as explained above).

In the paper Steinberg teach ion-selective monolayer membranes based on self-assembling tetradentate ligand monolayers on gold electrodes and discuss the nature of the ionic selectivity. The authors showed that monolayer membranes comprising the ligand TBEA (2,2'-thiobisethyl acetoacetate) and an inert blocking component (OM (n-octadecyl mercaptan), OTS (n-octadecyl trichlorosilane), or a combination thereof) on Au electrodes provide a unique example of organized monomolecular systems designed to perform a specific function, recognize and provide a selective electrochemical response for certain ions. The performance of these systems derives from their ability to fulfill 2 functions simultaneously: (1) selectively binding certain ions while (2) denying other ions access to the electrode. Thus, highly selective responses for certain divalent ions (e.g., Cu^{2+} or Pb^{2+}) were observed in the presence of large concentrations of other ions (e.g., Fe^{2+} or Fe^{3+}). The mechanism responsible for the ionic selectivity was studied by using two complementary types of experiments: ionic competition (i.e., the response to a certain ion in the presence of another ion in solution) and electrochemical behavior at intentionally induced monolayer pinholes. The pronounced ionic competition observed with TBEA-based monolayers on the one hand, and the lack of any competition at monolayer pinholes on the other hand, provide strong support for a selectivity mechanism based

on the binding of selected ions to TBEA molecules in the monolayer. The use of a polymerizable blocking component (OTS) substantially improves the lifetime of the monolayer membranes. Moreover, signs of deterioration of the performance can be easily reversed by applying "monolayer healing" procedures. Such monolayer systems may thus be useful as sensing elements for trace amounts of certain ions in the presence of large concentrations of nonbinding ions. A major conclusion of the present work concerns the selectivity considerations. As can be expected, the requirements for binding of an ion to TBEA in a monomer membrane are very different from the case of binding in solution. The 2-D arrangement of closely packed TBEA molecules in the monolayer membrane defines the coordination geometry and the cavity dimensions for ionic binding. The latter is an interesting example of a cooperative effect: inadequate matching of the ionic size of a bound ion to the cavity dimensions (either smaller or larger) introduces a local structural disturbance in the monolayer. This disturbance is transferred to neighboring molecules by virtue of the monolayer packing, giving rise to a lower effective binding constant. Such considerations, playing a prominent role in the case of TBEA monolayer membranes, must be taken into account in the design of future monolayer systems based on binding, penetration, and specific interactions. Some aspects of TBEA monolayer membrane systems still remain unclear, for example, the observation that $Fe(CN)_6^{4-}$ ions produce a sizable electrochemical signal at Au/(TBEA + blocking component) electrodes, which appear completely blocking toward nonbinding cations. This emphasizes the fact that penetration mechanisms in self-assembling monolayers are still not entirely understood. Relevant to the instant claims, Steinberg teaches on page 189 that a 2 hour exposure of the electrode to the OM provides a 98.1% surface coverage. A subsequent exposure for one hour raises the surface coverage to 99.8% and a final 30 minute exposure provides a coverage that no water or metal ion penetration can be detected. Page 190 gives various adsorption formats for the various components to include sequential treatment by the different components. Pages 193-194 present the monolayer healing process used. The first sentence under the 'Monolayer "Healing"' heading discusses the preparation of the monolayer by a common method in which the monolayer is formed in a single contacting step. The following sentence teaches that this is not necessarily the best method because the monolayers that result do not always possess the desired structural properties. This is because there are factors that are

likely to result in monolayer defects. The second and third paragraphs under this heading teach that a simple and effective procedure for improving the barrier properties of monolayers is through repeated adsorption steps in which the pinhole currents are removed by a mechanism that fixes the original defects.

In the paper Duan teaches immobilization of proteins on gold coated porous membranes via an activated self-assembled monolayer of thioctic acid. A new methodology for efficient protein (e.g., antibodies, enzymes, etc.) immobilization on microporous nylon membranes for use in a variety of bioanalytical systems is introduced. The method utilizes an activated self-assembled monolayer (SAM) of thioctic acid on gold coated forms of the membranes. Via a carbodiimide mediated reaction using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, the protein is anchored to the gold surface through an amide bond with the terminal carboxyl group of the adsorbed thioctic acid. The immobilization efficiency is high for a monoclonal IgG and the surface bound protein appears to be stable enough to resist any displacement by other proteins in a matrix as complex as serum. Immunological activity of immobilized antibody is retained as demonstrated via use of such membranes in colorimetric ELISA for human chorionic gonadotropin (hCG). The high protein immobilization efficiency, the high tensile strength of microporous nylon membranes, and the excellent electrochemical characteristics of gold make this approach very attractive for preparing biomembranes that should be useful in affinity chromatography, electrochemical immunosensing systems, flow-through enzyme reactors, etc (see page 205).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the detection compounds of Hilpert through a process as taught by Steinberg using the thioctic acid of Duan because of the ability to attach a complexing peptide to the metal as taught by Duan and cover the surface of the metal with a compound that will block its interaction with a sample as taught by Steinberg. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the metal complexing peptides of Fowlkes, Kay, Lopez or Wylie or other well known peptides and protein having the ability to bind heavy metals for the phytochelatin of Hilpert because of their equivalence as taught by Fowlkes and Kay or their known selectivity towards the metal as taught by Lopez or Wylie.

7. Applicant's arguments filed April 12, 2004 have been fully considered but they are not persuasive. Relative to claim 10, the format is still equivalent to a use claim since it fails to set forth steps of how the method is performed (see new claim 25). Relative to the art rejection using the Berggren paper, examiner points out that the last footnote on page 3657 clearly shows that the abstract of the paper has a publication date which is earlier than that of the complete paper. As a result examiner is no longer using the paper, but is relying solely on the disclosure of the abstract which does have a good publication date. Additionally the newly cited and applied Steinberg and Duan references show that contacting a formed monolayer with a compound that would fill in holes or defects in the monolayer to increase its blocking ability and using thioctic acid as a monolayer for immobilizing a protein or peptide to a gold electrode were known and provide advantages that would have motivated one of skill in the art to incorporate them into a device and method as taught by Hilpert.

8. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The art of record fails to teach or fairly suggest the use of the claimed surfactant during the coupling reaction of step d). the newly cited Liu reference clearly teaches using a surfactant or micellar solution in preparation of self assembled monolayers but does not teach or fairly suggest the specifically claimed surfactant.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to self assembled monolayers and electrode detection apparatus and methods using the monolayers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 7, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER